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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,226	02/14/2006	Yasuo Kunugiza	GRT/423-72	6159

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EXAMINER	
EPPS SMITH, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,226	KUNUGIZA ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Smith	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,9,11-18,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,9 and 21* is/are allowed.

6)☒ Claim(s) *8,11-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 8-9, 11-18 and 20-21 are presently pending for examination purposes.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

3. The rejection of claims 1-, 6, 8-9, and 11-18 under 35 U.S.C. 102(b) as being anticipated by Vasseur et al. (WO 94/23026), is withdrawn in response to Applicant's amendment to the claims.

4. The rejection of claims 1-9, 11-18 under 35 U.S.C. 102 (b) as being anticipated by Blumenfeld et al. (WO 9219731 A1), is withdrawn in response to Applicant's amendment to the claims.

5. The rejection of claims 1-9, 11-18 and 20 under 35 U.S.C. 102(b) as being anticipated by Ahn et al., is withdrawn in response to Applicant's amendment to the claims.

Claim Objections

6. The objection to Claim 10 as set forth in the prior Office Action is withdrawn in response to Applicant's cancellation of this claim.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. The metes and bounds of the term of "DNA derivative," with respect to the oligonucleotide of SEQ ID NO: 1 are vague and indefinite. The person of ordinary skill in the art would not be able to ascertain the scope of the claimed invention to the extent that the term DNA derivative is unclear.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 11-18, and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the staple oligonucleotide of SEQ ID NO: 1 for reducing the production of IL-1β in culture supernatant and synovial supernatant, does not reasonably provide enablement for using the staple oligonucleotide as a medicament for the treatment of the plurality of diseases recited in the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The scope of the claimed invention comprises the use of the staple oligonucleotide of claim 1, having undefined ligation status, for use as a medicament, particularly for the prevention, treatment or improvement of inflammation, an allergic disease, an autoimmune disease, a central disease, reperfusion injury in a ischaemic disease, worsened prognosis after organ transplantation or organ surgery, or restenosis after percutaneous transluminal coronary angioplasty (PTCA), and furthermore for improving any disease against which a transcription factor inhibitor, an antisense or an siRNA is efficacious.

The scope of the claims therefore encompasses a plurality of diseases, however the specification as filed provides only guidance for using the staple of oligonucleotide of SEQ ID NO: 1, for reducing the level of IL-1 β in culture. Furthermore, the claims do not recite any degree of ligation, however, it is clear that changes in the degree of ligation alters the ability of the staple oligonucleotide to reduce the level of IL-1 β in culture.

In regards to the use of antisense or siRNA for therapeutic purposes, at the time of the instant invention there was and remains a high degree of unpredictability associated with the in vivo use of staple-type/antisense/siRNA type compounds. For example, the prior art teaches that there is significant unpredictability associated with attenuating expression of a target gene in all types of cells, including mammalian cells, by RNA interference (RNAi). While it is recognized that introduction of dsRNA that is targeted to a specific gene may result in attenuation of expression of the targeted gene, the degree of attenuation and the length of time that attenuation is achieved is not predictable. Caplen et al. (Gene 2000, vol. 252, p.95-105) provide evidence of the unpredictability of dsRNA attenuation of a targeted gene in vertebrate cells *in vitro*. Caplen et al. report that although dsRNA inhibits gene expression in cultured *Drosophila* cells, screening of three commonly used cell lines from three different species: human, hamster, and mouse, using cells expressing transgenes both transiently and permanently, produced mixed results.

Additionally, RNA interference is recognized in the art as not enabled for therapeutic purposes. Caplen (2003) points out that, even post filing in 2003, "Many of

the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system…". (see page 581) Those of skill in the art of RNA interference are optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant application, the field recognizes that therapeutic methods are not yet effective. Thus, the post-filing art clearly suggests that administering dsRNA, either *in vitro* or *in vivo*, to attenuate expression of target genes is not a reproducible or predictable art.

RNA interference therapeutic methods encounter the same problems long recognized in other antisense/nucleic acid based therapies, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. The problems of nucleic acid based therapies are well known in the art. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000, vol 6, p 72-81) and Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects. These references discuss the problems of nucleic acid based therapies in reference to

antisense and gene therapy methods, however, as pointed out in Caplen (2003), RNA interference encounters similar problems as other nucleic acid based therapies.

Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), “Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in any type of cell, with a resultant therapeutic outcome, as claimed. The specification provides cell culture examples, these examples are generally not predictive of *in vivo* inhibition and corresponding production of disease prevention, treatment or improvement.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of staple oligonucleotide into any type of cell, either *in vivo* or *in vitro*, by the broadly disclosed methodologies of the instant invention, would result in successful attenuation/inhibition of a target gene, and furthermore, the treatment, prevention, or improvement of the broad class of diseases recited in the instant claims. One of skill in the art would not know how to deliver the staple oligonucleotides of the invention to an organism in such a way that would ensure an amount sufficient to attenuate expression of a target gene is delivered to the proper cell.

Conclusion

12. Claims 1, 9 and 21 are allowable over the prior art searched.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner
Art Unit 1633

/J. L. E./
Primary Examiner, Art Unit 1633